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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,604	08/18/1999	RAGUPATHY MADIYALAKAN	AREX-P03-004	6693

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Matthew P Vincent
Ropes & Gray
One International Place
Boston, MA 02110

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/376,604	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *276-338* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *276-281,283-321 and 323* is/are rejected.

7)☐ Claim(s) *c* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/26/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 113, 117-120, 125, 129-131, 133-135, 137-139, 129-131, 133-135, 137-139, 141-144, 170-174, 180-182, 187, 190-193, 195, 197-204, 206-209, 236, 237, 239, 241-244, 247-251, 254-275 have been canceled. Claims 279-338 have been added. Claims 276-338 are pending and under consideration.

Claims 276-281, 283-321, 323 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an oncological disease comprising administering to a host a complex formed from CA125 and the monoclonal antibody B43.13 or antigen-binding fragment thereof that binds to CA125, and wherein the complex induces host antibodies and cytotoxic T-cells reactive with at least one other epitope of the tumor associated antigen, does not reasonably provide enablement for the administration of any other complex of a soluble tumor antigen and a monoclonal antibody or antigen-binding fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized by In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claim require the induction of a therapetuic host immune response against any oncological disease comprising the stimulation of a multi-epitopic immune response carried out by the administration of the soluble antigen of CA125, CA19.9, CA15.3 or PSA and a monoclonal antibody that binds thereto. The immune response encompassed by claim 276 and 278, and depdnent claims thereof requires a cellular immune response which includes the generation of cytotoxic T lymphocytes. The specification and art of record indicates that administration of the Mab 43.13 which bind to circulating tumor antigen in the blood of ovarian cancer patients resulted in the unexpected long survival times of these patients. The specification teaches that the presence of the circulating tumor antigen in the blood complexed with the administered antibody. The specification teaches that the administration of the antigen-antibody complex rather than the antigen alone results in a humor response comprising antibodies which bind to multiple epitopes on the antigen, as well as a T-cell response in conjunction to the humoral response. The art teaches that Th1 cell-mediated immunity is critical for the induction of an anti-tumor response (Nishimura et al, Cancer Chemother Pharmacol, 2000, Vol. 46, suppl. pages S52-S61, cited in a realted application). The art teaches that cancer patients are often tolerized to their respective tumors (Sotomayor et al, Critical Reviews in Oncogenesis, 1996, Vol. 7, pp. 433-456,cited in a related application). The art teaches that the presence of the antibody complexed to the antigen changes the recognition of the immunological determinants within the antigen (Simitsek et al, J Exp Med, 1995, Vol. 181, pp. 1957-1963, cited in a prior action; Watts et al, J Exp Med, 1993, Vol. 178, pp. 1495-1463). The art teaches that tolerance to a protein involves tolerance to the immunodominant determinants rather than the subdominant determinants (Cibotti et al PNAS, 1992, Vol. 89, pp. 416-420, cited in a related action). It is noted that the abstract of Pani et al (Immunological Investigations, 1994, Vol. 23, pp. 337-346, cited in a realted action) reports that "tolerance to a self protein shows the same phenomenon seen for non self proteins". The art teaches that disruption of the determinant hierarchy (dominant versus subdominant) can result in the priming of an immune response to a subdominant or cryptic self-determinant (Benichou et al, 1994, Vol. 6, pp. 131-138, cited in a realted action). However, neither the specification nor the art teaches how to expose subdominant epitopes on soluble tumor antigens that will be effective to treat an oncological disease. It is noted that a monoclonal antibody would bind only to a single epitope on a tumor

antigen. According to the art, this would suppress the recognition of that epitope when taken up by an antigen presenting cell due to the physical binding of said antibody, and the persistence thereof within said cell. In order for the treatment to be effective, immune recognition of a subdominant epitope of the tumor antigen must effectively generate cytotoxic T-cells that recognize and cell of the oncological disease. The specification provides no teachings on how to select a subdominant epitope(s) for enhancement by the suppression of the immunodominant epitope in an antibody-antigen complex. It is noted that the administration of the antigen antibody complex can result in the priming of the immune response to subdominant epitopes of the soluble tumor antigen which are not accessible on the tumor surface by virtue of the conformation of said tumor antigen while part of the tumor surface.

The art teaches that the generation a quantifiable CTL in the peripheral blood of cancer patients, such a CTL response, is not associated with clinical evidence of tumor regression (Lee et al, Journal of Immunology, 1999, Vol. 163, pp. 6292-6300, cited in a realted action). Further, Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870, cited in a realted action) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). Thus, there appears to be no nexus between the presence of CTL in vivo and an anti-tumor response in an individual, and further, there is not teachings for the selection of a subdominant epitope wherein priming to said subdominant epitope can result in a CTL which recognizes tumor antigen on the tumor cell surface.

The prior art teaches that tumor cells are phenotypic ally less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the

tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4, cited in arealted application).

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105, cited in a realted action) and the abstract of Algarra et al, International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102, cited in a realted action) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed complex upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teach that the failure of methods of treating cancer comprising the administration of compositions which are designed to render an immune response against the tumor based on recognition of the tumor antigen is due to the failure to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

The post-filing date art teaches that a therapeutic host immune response was elicited in human patients receiving multiple doses of B43.13 (Schultes et al, Cancer Immunol Immunother, 1998 June, Vol. 46, pp. 201-212, cited in a related action). The teachings of the specification regarding the B43.13 antibody do not provide a nexus for the use antibodies which bind to alternate epitopes within CA125, or antibodies that bind to CA19.9, CA15.3 and PSA. The specification does not provide any guidance for the selection of a different antibody which binds to CA125, nor of antibodies which bind to epitopes of CA125 that differ from the epitope bound by Mab 43.13. Thus, while other antibodies that bind the same epitope of Mab 43.13 would be expected to function within the same method, there is no assurance from the instant specification regarding the criteria for selecting other antibodies which bind to differing epitopes of CA125 which would evoke host cytotoxic T-cells and antibodies recognize alternate epitopes of CA125. It is noted that the instant specification claims priority to WO 97/42973, filed May 15, 1996 and should be enabled as of the effective filing date sought. Madiyalakan et al (WO9965517, page 12, lines 12-30) teach:

Stimulation of T cells reactive with subdominant or cryptic epitopes of self proteins has been suggested as an important factor in inducing immunity to a predetermined antigen, e. g., an antigen involved in a disease or condition such as cancer or auto-immunity. Antibody-enhanced or-altered presentation of an antigen, such as CA125, in an antibody complex, e. g., bound to MAb-B43.13, by B cells (antibody specific), or macrophages or dendritic cells (both receptor mediated), may result in presentation of different peptides to the immune system than those obtained by presentation of the antigen alone. This can lead to sufficient presence of antigen-specific peptides from subdominant or cryptic epitopes which may in turn stimulate low affinity T cells that escaped clonal deletion in the thymus or re-stimulate T cells which were suppressed. The immune response induced by exogenous administration of an antibody to a circulating self-antigen can therefore be compared to that observed in auto-immune diseases. This may also explain why presence of immune complexes of antigen with autologous human antibodies is often not correlated with improved survival. Human B cells recognize preferably immune-dominant epitopes of the antigen, leading to presentation of epitopes against which T cells were formed during fetal development. Murine antibodies on the other hand, recognize immune-dominant epitopes in mice which are not necessarily equivalent to the human immune-dominant epitopes.

Thus, the teachings of the post-filing date art indicate that it is necessary to target subdominant epitopes of the CA125 antigen and that epitopes targeted by murine antibodies are "not necessarily equivalent" to the human dominant epitopes. Thus, the post filing reference teaches the importance of targeting an epitope which is not a dominant epitope in order to elicit antibodies and immune recognition against subdominant epitopes and that not all murine antibodies will possess the criteria of targeting an epitope which is not a dominant human epitope. without this information published in 1997, it would be undue experimentation in order to screen all possible antibodies, including antibodies from a multitude of experimental hosts and human antibodies, for the ability to evoke antibodies to a different epitope on CA125 than that bound by the antibody or T-cell recognition of CA125.

The specification provides evidence that adminisntraiton of the Alt-3 antibody in a murine experimental model induced complement-mediated cytotoxicity (page 59, lines 12-17). The specification teaches that administration of the Alt-4 antibody in an experimentla murine

model was effective at inhibiting inflammation (page 63, lines 15-23). The specification teaches the administration of anti-PSA antibodies in a murine tumor model and the resulting "negative correlation between Ab3 levels and the number of tumor foci in the lungs" (page 63, lines 5-9). This fails to provide a nexus for the inducion of an effective anti-tumor response in a patient with a natrually occuring tumor, or the induction of an effective anti-tumor response in a huamn patient. Regarding the anti-PSA antibodies and the impact on tumor foce in the murine system, Goldenberg, (U.S. 6,096,289, column 11, lines 43-48) teaches that it is difficult to extrapolate from animal experiments to the clinic because rodent models do not bear the same distribution of target tumor-associated antigens in their blood and tissues as is true for humans, and that the tumor uptake of antibodies in the rodent model is hundreds to thousands and more higher than in humans. Further, it is well recognized in the art that clinical results on patients do not reflect the results of animal models. Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664, cited in related application) teach that encouraging animal model studies lead to clinical trails, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676, cited in a realted application) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing. Thus, there is no nexus between the impact on lung tumor foci development and a therapetuic response in a human patient.

Claims 277 and dependnt claims thereof are drawn to inducing an effective host humoral response against the antigen(s). this includes methods where only a humoral immune response is generated with a cellular immune response. However, the art recognizes that an effective anti-tumor immune response requires a cellular immune response. Kedar and Klein ('Cancer Immunotherapy' In: Advances in Cancer Research, 1992, vol. 59, pp. 245-323, cited in a related application, especailly pages 248-250, under the heading of "Tumor Immunogenicity and T-Cell Response").

Due to the unreliability of the art as discussed above, the lack of a working example which demonstrates the successful treatment of a subject having a natrually occuring tumor, and/or a human cancer pateint, with an antigen antibody complex beyond that of Mab 43.13

bound to soluble CA125, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the broadly claimed method.

Claims 286, 287, 292, 306, 307, 312, 326, 327 and 332 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to teach or provide complete evidence either that the claimed antibodies are known and readily available to the public or complete evidence of the deposit of the antibodies . In order to proactice the methods of claims 286, 287, 292, 306, 307, 312, 326, 327 and 332 , it is required that one of skill in the art have possession of the exact claimed antbodies. Possession can be fulfilled if the antibodies are publicly available or can be reproducibly isolated from nature without undue experimentation. For example, Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." It is unclear that one of skill in the art could derive an antibodies which are identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies.

Because one of ordinary skill in the art could not be assured of the availablity to practice the invention as claimed in the absence of the availability of the claimed monoclonal antibodies, a suitable deposit of the hybridomas producing the claimed anrtibodies for patent purposes, evidence of public availability of hybridomas producing the claied antibodies or evidence of reproducibility without undue experimentation of the claimed monoclonal antibodies is required.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits have been accepted by an International Depository authority

under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is neccessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendancy of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforcable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Ammendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing identical monoclonal antibodies as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claims 276-282, 299-302, 313-315, 319, 334 and 335 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30, 71, 76, 85-88, 96, 98-100, 103-114, 117-119 and 123-128 of copending Application No. 09/152,698. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '698 application are obvious over the instant claims. It can be readily envisaged that the antigen-antibody complexes of the '698 application is being formed in vivo upon administration of the claimed antibodies in the instant claims, but the claims require that CA125 be present in the host's serum.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.

8/6/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER